Second generation dihydropyridine calcium channel blockers in chronic heart failure.

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SUMMARY

CHF is a progressive disease which has a high morbidity and mortality despite treatment with ACEI, diuretics and digoxin. With the aging of the population and the progress in the treatment of ischemic heart diseases and hypertension the number of patients with CHF is increasing, making CHF a large socio-economic and epidemiological problem. In the pathophysiology of CHF vasoconstriction is thought to play a key role. Adjunctive vasodilation, on top of the above mentioned treatment, may be potentially useful. Calcium channel blockers are arterial vasodilators and are used in the setting of ischemic heart disease and hypertension. Since hypertension and ischemic heart disease are the underlying etiology in 60-70% of the patients with CHF, expectations were high regarding the potential of calcium channel blockers for CHF. However, in clinical practice the first generation calcium channel blockers, diltiazem, verapamil and nifidipine gave overall results which were thought to be due to their negative inotropism and neurohumoral activation. Second generation calcium channel blockers (mainly belonging to the dihydropyridines class) were expected to be of more value in patients with CHF as they were vascular selective, thus not inducing negative inotropism at dosages already giving clinically relevant vasodilation. Furthermore they have a slow onset of action to prevent reflex sympathetic stimulation. In this thesis we sought whether these newer dihydropyridines could be of value in patients with CHF. In the appendices clinical, experimental studies, and a review article are reported. The clinical studies in patients with CHF evaluated the effects of long term dihydropyridines treatment on cardiopulmonary exercise parameters and on plasma neurohormones (appendix 1,2 and 4), on acute and long-term hemodynamics (appendix 2-4) and on diastolic function (appendix 3). Effects were tested both on top of ACEI (appendix 2,4) or versus ACEI (appendix 1,4). The predictive and prognostic value of submaximal exercise testing is reported in appendix 5. Experimental studies in rats with an experimental myocardial infarction are presented in appendices 6 and 7. In these studies the effect on endothelial function, heart rate variability and plasma neurohormones (appendix 6) and on β-adrenoceptor density (appendix 7) were studied.

In appendix 1, the results of a double blind, randomized study comparing the dihydropyridine felodipine, and the angiotensin converting enzyme inhibitor enalapril are presented. All 46 patients had symptoms of CHF despite treatment with diuretics and digoxin. Patients had a peak oxygen consumption below 20 $ml.min^{-1}.kg^{-1}$ and a left ventricular ejection fraction less than 0.40. After 16 weeks of therapy there were no statistically significant differences in peak oxygen consumption (felodipine +1.6, enalapril +2.5 $ml.min^{-1}.kg^{-1}$) and exercise tolerance (felodipine +61 seconds, enalapril +64 seconds). Quality-of-life parameters were affected slightly better by felodipine than by enalapril ($p<0.05$). Plasma norepinephrine decreased by 143 $pg.ml^{-1}$ with enalapril and by 12 $pg.ml^{-1}$ with felodipine (p=NS between groups). With regards to safety no influence was seen on ambulatory electrocardiographic monitoring or laboratory data. Felodipine treated patients had significantly more vasodilatory induced

side effects. These data suggest that 16 week treatment of felodipine or enalapril has comparable effects on exercise parameters in patients with CHF. Overall neurohumoral activation was not observed with either drug.

In appendix 2 a placebo-controlled, double-blind, parallel group study of 8 weeks evaluating the efficacy and safety of the dihydropyridine calcium channel blocker lacidipine in 25 patients with CHF is presented. Results from cardiopulmonary exercise tests, invasive hemodynamics, echocardiography and neurohormones at rest, assessed at baseline and after 8 weeks therapy, were analyzed. All patients were symptomatic despite treatment with ACEI, digoxin and diuretics. Treatment with lacidipine 4 mg once daily as compared to placebo treatment significantly improved peak oxygen consumption ($p<0.02$), cardiac index ($p<0.01$) and stroke volume ($p<0.03$) paralled by a decrease in systemic vascular resistance ($p < 0.03$) and arteriovenous oxygen content difference ($p< 0.01$). Lacidipine did not influence plasma norepinephrine, plasma renin activity or aldosteron. The global assessment of efficacy by both investigator and patient suggested a trend for improvement on lacidipine treatment. Lacidipine was generally well tolerated, although worsening of CHF occurred in 1 patient. The results from this study with lacidipine in patients with CHF demonstrate that a dihydropyridine may be of additive value as an adjunct to optimal, including ACEI, therapy in CHF patients.

In appendix 3, an acute hemodynamic study is reported comparing the archetype dihydropyridine, nifedipine, with a second generation dihydropyridine isradipine. In 20 patients with left ventricular ejection fraction below 0.40 measurements with a nuclear stethoscope were taken at rest and during right atrial pacing. The drugs were given in equihypotensive dose. Both systolic and diastolic parameters improved equally with isradipine and nifedipine. Left ventricular ejection fraction and cardiac output increased due to peripheral vasodilatation. A negative inotropic effect was noted in patients at rest with both medications, but not during pacing-induced ischemia. With either medication, the time constant of relaxation and the end-diastolic elasticity constant decreased during pacing, indicating improvement in diastolic function.

In appendix 4 a review is given of clinical studies, reported since 1990, in patients with CHF and treated with a second generation dihydropyridine calcium channel blocker. This review sought to evaluate the value of these drugs in patients with CHF. In over 2000 patients with CHF, no consistent beneficial effect of second generation dihydropyridine treatment was observed with regard to exercise tolerance or functional capacity. Plasma neurohormones were not significantly affected although it appears that a consistent increase in plasma renin activity can be observed. In general the data do not support the use of these drugs as standard treatment of CHF. On the other hand, in general no worsening of CHF was seen with these second generation DHP and it may be suggested that these drugs can be safely given to patients with CHF, who need additional treatment for angina pectoris or hypertension.

From our clinical studies, and reports in literature, several questions arose regarding the mechanism by which second generation dihydropyridines may be of value and another question regarded the use of cardiopulmonary exercise testing in patients with CHF. First of all we were disappointed in the lack of sensitivity of peak oxygen consumption or highest comparable oxygen consumption to detect differences between treatment strategies. To test whether other cardiopulmonary exercise parameters could be of predictive and prognostic value in patients with CHF we conducted a study (appendix 5). In this study of 96 patients with CHF and an ejection fraction < 0.45 (mean 0.27) we analysed the relationship between initial exercise parameters and peak oxygen consumption and prognosis. These initial exercise levels appears better to present a patients everyday activity. Significant differences in several initial stages parameters were seen. The parameters oxygen pulse and ventilation equivalent for oxygen remained as independent predictors of peak oxygen uptake. In a multivariate Cox proportional hazards model this predicted (from the intial stages) peak oxygen uptake remained as an independent predictor of mortality. Thus the initial 6 min parameters of a cardiopulmonary exercise test may have independent value in the assessment of clinical severity and prognosis in patients with CHF.

Another question that remained after the clinical studies was whether improvement in endothelial function or upregulation in β-adrenoceptor density could attribute to the effects of amlodipine in patients with CHF. This was studied in rats after a myocardial infarction had been induced. In these experiments treatment was started 10 days after infarction and lasted 8 weeks. The rats were sacrificed and the post mortem studies were performed. With regard to endothelium dependent vasorelaxation of the aorta amlodipine did not have a beneficial effect as compared to the control group (appendix 6) and no differences in plasma neurohormones were found. Amlodipine tended to increase coronary flow as tested in the Langendorff model. In the other experiment, evaluating a potential effect by amlodipine on β-adrenoceptor density or heart rate variability, no differences could be demonstrated on these parameters (appendix 7). So our animal experiments could not confirm our hypothesis.

The following conclusion can be drawn from this thesis:

1 Available data on second generation dihydropyridines in patients with CHF do not support the use of these drugs primarily for the treatment of CHF.

2 Second generation dihydropyridines do not increase mortality or morbidity in patients with compromised left ventricular function.

3 Regarding neurohumoral activation, second generation dihydropyridines do not induce significant neurohumoral activation nor do they suppress neurohumoral activation. In addition, other parameters such as heart rate variability and ß-adrenoceptor density were unaffectected in our preclinical experiments, but matching clinical data are not (yet) available on this issue.